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PRE-APPEAL BRIEF REQUEST FOR REVIEWDocket Number (Optional)
9516-086-999

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name _____

Application Number
10/534,324

Filed
February 24, 2006

First Named Inventor
Jerome B. Zeldis

Art Unit
1612

Examiner
Sznaidman, Marcos L.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

☐

applicant/inventor.

/Kam W. Law/

Signature

☐

assignee of record of the entire interest.

See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

Kam W. Law

Typed or printed name

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attorney or agent of record.

Registration number _____

852-3189-7371

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attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34 44,205

November 19, 2010

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒

*Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis

Confirmation No.: 9742

Application No: 10/534,324

Group Art Unit: 1612

Filed: February 24, 2006

Examiner: Sznaidman, Marcos L.

For: METHODS OF USING
CYCLOPROPANECARBOXYLIC ACID {2-
[(1S)-1-(3-ETHOXY-4-METHOXY-
PHENYL)-2-METHANESULFONYL-
ETHYL]-3-OXO-2,3-DIHYDRO-1H-
ISOINDOL-4-YL}-AMIDE FOR THE
TREATMENT AND MANAGEMENT OF
MYELOPROLIFERATIVE DISEASES

Jones Day Docket No.: 9516-086-999
CAM 501872-999085

REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant respectfully requests a Pre-Appeal Brief Request for Review for at least the following reasons.

- I. the Examiner erred in facts and in alleging that the prior art references teach or suggest that any TNF- α inhibitor can treat a myeloproliferative disease (“MPD”); and
- II. the Examiner erred in dismissing teaching away in the prior art reference.

I. The Examiner erred in alleging that the prior art references teach or suggest that any TNF- α inhibitor can treat MPD

The Examiner has rejected (a) claims 1, 5, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* (*Cancer Chemotherapy and Pharmacology* (2002) 50:237-242) in view of Man *et al.* (WO2001/34606); (b) claims 6 and 11 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.* (*British Journal of Haematology* (2001) 115:313-315); and (c) claims 3 and 7-9

under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.* (*Blood* (1985) 66:373-379). *See* Final Office Action mailed June 4, 2010, pages 3-4.

The instant claims recite, *inter alia*, a method of treating or managing a MPD, which comprises (a) administering to a patient having the MPD a therapeutically or prophylactically effective amount of cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide “Compound A”, or a pharmaceutically acceptable salt thereof for a period of time followed by rest; and (b) repeating step (a), wherein the MPD is selected from the group consisting of polycythemia rubra vera (“PRV”), primary thrombocythemia (“PT”), chronic myelogenous leukemia (“CML”) and agnogenic myeloid metaplasia (“AMM”), and wherein the therapeutically or prophylactically effective amount is from about 5 mg to about 50 mg per day.

The Examiner has admitted that (1) Tsimberidou *et al.* does not teach or suggest the treatment of AMM or any MPD with Compound A; and (2) Tsimberidou *et al.* merely teaches a method of treating AMM with Etanercept (aka Enbrel). *See* Office Action dated November 12, 2008, page 10, lines 10-21; and Office Action dated December 28, 2009, page 6, lines 3-11. The Examiner has also admitted that Man *et al.* merely teaches that Compound A is a TNF-alpha inhibitor. *See* Final Office Action dated April 1, 2009, page 7, lines 16-18; and Office Action dated December 28, 2009, page 6, lines 11-13. But Man *et al.* is silent about AMM or any MPD. Therefore, Man *et al.* does not cure the defects of Tsimberidou *et al.* because Man *et al.* does not teach or suggest the treatment of AMM or any MPD with Compound A.

However, the Office has maintained the incorrect position throughout the entire prosecution history of this case that at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute Etanercept or thalidomide disclosed in Tsimberidou *et al.* with Compound A (a non-polypeptide) of Man *et al.* with an expectation of success. *See* Office Action dated November 12, 2008, page 11, lines 8-16; Final Office Action dated April 1, 2009, page 7, line 19 to page 8, line 4; and Office Action dated December 28, 2009, page 7, lines 3-10. This incorrect position is based on the Examiner’s error in alleging that any TNF-alpha inhibitor can be substituted with another TNF-alpha inhibitor for treating MPD with an expectation of success. However, this

allegation is incorrect because not all TNF-alpha inhibitors can be used to treat MPD for the following reasons.

Tsimberidou *et al.* on page 240, col. 1, lines 28-32 states that “(c)urrent treatment options other than allogeneic stem cell transplantation [21], including hydroxyurea [33], α -interferon [19, 37], androgens [6], thalidomide [3, 8], and splenectomy [2] are ultimately ineffective in patients with AMM and novel agents are required.” The issue is which term, “current treatment options” or “allogeneic stem cell transplantation,” includes hydroxyurea, α -interferon, androgens, thalidomide and splenectomy. Throughout the entire prosecution history of this case, the Office has maintained the incorrect position that “allogeneic stem cell transplantation” includes hydroxyurea, α -interferon, androgens, thalidomide and splenectomy. *See* Final Office Action dated April 1, 2009, page 10, lines 1-6; and Final Office Action dated June 4, 2010, page 7, lines 6-16. Please note that “allogeneic stem cell transplantation” scientifically cannot include thalidomide, hydroxyurea, α -interferon, androgens and splenectomy because thalidomide and the others are different from stem cell transplantation. This is not a colorable difference in interpretation, but is, instead, a clear error in fact as explained above.

In contrary to the Office’s incorrect interpretation, Tsimberidou *et al.* actually teaches that, other than allogeneic stem cell transplantation, the current treatment options including thalidomide (a TNF-alpha inhibitor) are ultimately ineffective in treating patients with AMM.

Further, throughout the entire prosecution history of this case, the Office has maintained the incorrect position that Tsimberidou *et al.* teaches that Etanercept (*aka* Enbrel) and any TNF-alpha inhibitor such as thalidomide are effective in treating AMM. *See* Office Action dated December 28, 2009, page 7, lines 3-10; and Final Office Action dated April 1, 2009, page 9, line 20 to page 10, line 6. As explained above, Tsimberidou *et al.* teaches that thalidomide, a TNF-alpha inhibitor, is “ultimately ineffective in patients with AMM.” Further, the abstract section of Tsimberidou *et al.* at page 237, col. 1 discloses that “no objective response was seen in 22 patients (88%)...” More importantly, in view of all data including those 3 patients (12%) showing progression, the conclusion section of Tsimberidou *et al.* at page 237, col. 2 concludes that “no responses were noted” with Enbrel (*aka* Etanercept) treatment of patients having refractory hematological malignancies including MPD. In summary, the Office has erred in alleging that Tsimberidou *et al.* teaches that Enbrel and other TNF-alpha inhibitors such as thalidomide are effective in treating AMM.

Further, skilled persons in the art recognize that not all TNF-alpha inhibitors are effective in treating AMM. For example, the article (Ramanarayanan *et. al.*, “*Abrogation of tumor necrosis alpha (TNF-alpha) pathway by anti-TNF therapy in hematological malignancies*,” *J. Clin. Oncol.*, 27:15s, 2009 (suppl; Abstr. No. 7093)) which was submitted with the amendment dated April 8, 2010 by Applicant provides evidence that the Examiner cannot rely on TNF- α activity to support the current rejections. Ramanarayanan *et. al.* reviewed the literature of phase I and II studies involving anti-TNF-therapy, and explored the activity and tolerance of TNF- α inhibitors in various hematological malignancies including MPD. Ramanarayanan *et. al.* concluded that anti-TNF- α therapy by itself does not induce therapeutic response and that combination therapy with TNF- α inhibitors has to be evaluated to determine their role in MPD. Therefore, Ramanarayanan *et. al.* teaches that not all TNF- α inhibitors can treat MPD.

However, the Examiner discounted the facts of Ramanarayanan *et. al.* and, based on incorrect interpretation of facts, insisted that skilled artisans will still have a motivation to combine the teachings of Tsimberidou *et al.* and Man *et al.*, despite Ramanarayanan *et. al.* suggests otherwise. The reasoning of the PTO is that contradictory results allegedly are very common in science. *See* Final Office Action dated June 4, 2010, page 5, lines 10-14. However, the PTO failed to provide any evidence to support its position. Further, the Examiner contended that Ramanarayanan *et. al.* simply talks about MPD in general without specifying any particular MPD disease, and conveniently ignored the fact that the instant claims recite a method of treating MPD, and that the cited reference Man *et al.* is silent about both MPD in general and any MPD disease in particular. *See* Final Office Action dated June 4, 2010, page 5, lines 6-9.

In summary, the Examiner made clear errors in facts mentioned above and in alleging that the prior art references teach or suggest that that Etanercept, thalidomide and any TNF- α inhibitor can treat MPD.

II. The Examiner erred in dismissing Teaching Away In The Prior Art Reference

As mentioned above, Tsimberidou *et al.* teaches that (1) except allogeneic stem cell transplantation, the current treatment options including thalidomide (a TNF-alpha inhibitor) are ultimately ineffective in treating patients with AMM; and (2) no responses were noted with Etanercept treatment of patients having refractory hematological malignancies including

MPD. Therefore, Tsimberidou *et al.* teaches away from the claimed method which comprises, *inter alia*, administering to a patient having MPD a therapeutically or prophylactically effective amount of Compound A, a TNF-alpha inhibitor. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. “A claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results.” *Crocs, Inc. v. U.S. International Trade Commission*, 598 F.3d 1294 (Fed. Cir. 2010). (Emphasis added.) see also M.P.E.P. § 2141.02(VI) (“A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.”).

For at least the reasons set forth above, Applicant respectfully submits that the Examiner’s rejections of (a) claims 1, 5, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.*; (b) claims 6 and 11 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.*; and (c) claims 3 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.* are improper and should be withdrawn.

All previously filed responses are incorporated herein by reference in their entireties, including Responses filed February 12, 2009; July 8, 2009; and December 28, 2009. Applicant reserves the right to raise any issues or arguments made during the prosecution of this case in a Brief on Appeal or during any subsequent prosecution of this case.

Respectfully submitted,

Date: November 19, 2010

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